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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,496	01/14/2002	William S. Adney	NREL 99-45	6834

23712 7590 06/05/2007

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
06/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,496	ADNEY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,9-16,20-22 and 24-30* is/are pending in the application.

4a) Of the above claim(s) *15,16,27 and 28* is/are withdrawn from consideration.

5)☒ Claim(s) *11-14* is/are allowed.

6)☒ Claim(s) *6,7,9,10,20-22 and 24-26, 29, 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-7, 9-16, 20-22, 24-30 are currently pending and are present for examination. Claims 6-7, 9-16, 20-22, 24-30 drawn to polynucleotides and a method mutating the polynucleotide are now under consideration. Claims 15-16, 27-28 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants should note that this application has been transferred from Ex. Charles Patterson to the current examiner M.Rao.

Applicants' amendments and arguments filed on 3-20-07, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

This application claims priority to the parent application PCT/US00/19007 filed on 7-13-00 which in turn claims priority to US provisional application 60/143711 filed on 7-13-99. Examiner wishes to clarify whether applicants have filed the instant application as a continuation of the above PCT application or as a PCT 371 National stage application of the above PCT application.

Specification and Sequence compliance

The disclosure is objected to because of the following informalities: Sequence compliance. Appropriate correction is required.

Applicants have addressed the concerns raised by the previous examiner regarding sequence compliance. However, the issue still continues to confusing to this examiner as well. Initially this application was filed with four polypeptide sequences. Later a new sequence listing was filed with a full length polynucleotide sequence and a total of 120 sequences. Still later, another sequence listing was filed with one polynucleotide and one polypeptide sequence and 94 other short sequences with a total of 96 sequences. Recently it appears applicants have filed yet another sequence listing with a total of 97 sequences. It appears that applicants have added and removed sequences without proper explanation. In the most recent filing, Applicants have not filed a paper sequence listing and draw the attention of the examiner to the electronic copy adding more to the above confusion. It is not clear to the Examiner why applicants have removed the initially filed four polypeptide sequences and whether the current polypeptide sequence is one of them. As stated above applicants have addressed the issue however, it is still very confusing. This examiner urges the applicants to file a paper copy of the sequence listing in order for him to understand the sequence issue raised by the previous examiner. This examiner also urges applicants to explain to him why sequences have been added and removed and where can he find support for the added and removed sequences. Even though the new matter rejection has been withdrawn at this time by the current examiner, upon reviewing the paper sequence listing and the explanation provided by the applicant this examiner may reinstitute the same rejection if required and the office action will be made final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 26 and claims 7, 9, 10, 20-22, 24-25, 28-30 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 26 recite the phrase "encoding a variant cellobiohydrolase that is mutated with respect to a wild-type cellobiohydrolase of SEQ ID NO: 5...comprising a proline substituted at position 8". It is not clear to the Examiner as to what applicants mean by the above phrase. It is not clear whether the encoded variant will have an identical amino acid sequence as that of SEQ ID NO:5 except for position 8 or whether the variant will have any amino acid sequence except that the position 8 amino acid is a praline. Examiner seeks clarification. For purposes of examination, examiner has considered the phrase broadly to mean that the variant comprises any amino acid sequence except for the amino acid at position 8 to be a proline.

Claim 6 and claims 7, 9, 10, 20-22, 24-26, 28-30 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 26 recite the phrase "for improving the functionality of the variant". It is not clear to the Examiner as to what "functions" are encompassed by the term "functionality". It is not clear whether it means the functionality refers to the hydrolytic action, temperature stability, pH stability etc. Examiner requests clarification.

Claims 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20-22 recites the limitation "thermostability" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7, 9-10, 20-22, 25-26, 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant polynucleotide encoding a polypeptide with SEQ ID NO:5 except for the amino acid at position 8 which is substituted with a proline and having cellobiohydrolase activity and further comprising substitutions at several other listed amino acid positions activity, does not reasonably provide enablement for any polynucleotide encoding any amino acid sequence, having cellobiohydrolase activity but for a proline at position 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6-7, 9-10, 20-22, 25-26, 29-30 are so broad as to encompass any for any polynucleotide encoding any amino acid sequence, having cellobiohydrolase activity but for a proline at position 8. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a given polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a single cellobiohydrolase comprising SEQ ID NO:5. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides. The specification is limited to teaching the use of the polynucleotide which encodes SEQ ID NO: 5 as a cellobiohydrolase, to make variants of that polynucleotide but provides no guidance with regard to the making of any or all variants and mutants of any cellobiohydrolase encoding polynucleotides. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from an encoded polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would

require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within an encoded protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass variants of any polynucleotide encoding a cellobiohydrolase because the specification does not establish: (A) regions of the protein structure which may be modified without affecting cellobiohydrolase activity; (B) the general tolerance of cellobiohydrolase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

While the specification does provide guidance to make a variant of a cellobiohydrolase comprising SEQ ID NO:5 by way of substituting the amino acid at position at position 8 with a proline, the same specification does not provide support that performing the same in polynucleotides encoding any or all cellobiohydrolases. Current claims are simply not limited

to polynucleotides encoding the specific variant of SEQ ID NO:5 with a proline substituted at position 8 but to polynucleotides encoding any or all variants of SEQ ID NO:5. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications to the polynucleotide sequence encoding SEQ ID NO:5. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants traverse the above rejection arguing the specification provides guidance regarding the improved functionality of the polypeptide. While that may be so, the current argument in the rejection is that while claims are enabled for a polynucleotide encoding a specific variant of SEQ ID NO:5 comprising a proline substitution at psotion 8 (i.e., wherein the variant comprises the same amino acid sequence of SEQ ID NO:5 except for position 8), claims are not enabled for a polynucleotide encoding any variant of SEQ ID NO:5, wherein the variant comprises any amino acid sequence and also has proline at position 8. Applicants argue that Examples 1-6 demonstrate how improved variants were obtained and sequences provided indicate exemplary mutations made to achieve improved functionality and therefore, claim 6 is enabled according to the Wands factors described above as Applicants have provided more than sufficient direction in the specification and provided multiple examples

describing the improved variants, because the quantity of experimentation needed to make or use the improved variants is limited based on the Applicants' disclosure, and because the level of one of ordinary skill in the art is such that assays for determining enzymatic activity are well known. Examiner respectfully disagrees. The claims as written read on polynucleotides encoding any variant of SEQ ID NO:5 including a proline substitution at position 8. The specification fails to provide guidance to make any variant of SEQ ID NO:5. Therefore, without specific guidance one of ordinary skill in the art would be subject to the undue experimentation of making and testing an infinite number of variant polynucleotides encoding cellobiohydrolase polypeptides having an improved functionality.

Claims 6-7, 9-10, 20-22, 25-26, 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules encoding any mutants and variants of SEQ ID NO:5 wherein said mutant comprise any amino acid sequence except for the amino acid at position 8 which is mutated to a proline.

The specification does not contain any disclosure of the structure of all DNA sequences encoding any mutants and variants of SEQ ID NO:5 wherein said mutant comprise any amino acid sequence except for the amino acid at position 8 which is mutated to a proline. The genus of DNA molecules that comprise these above polynucleotides is a large variable genus with the potentiality of encoding many different proteins having different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

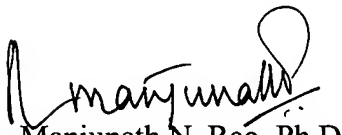
Conclusion

Claims 11-14 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

May 29, 2007